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131

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 211/34 — A1

(11) International Publication Number: **WO 97/32851**

(43) International Publication Date: 12 September 1997 (12.09.97)

(21) International Application Number: PCT/GB97/00643

(22) International Filing Date: 7 March 1997 (07.03.97)

(30) Priority Data:

9604943.2	8 March 1996 (08.03.96)	GB
60/016,986	7 May 1996 (07.05.96)	US

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(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: RESOLUTION OF THREO-METHYLPHENIDATE

(57) Abstract

A process for preparing substantially single enantiomer *d-threo*-methylphenidate, proceeds by means of a classical salt resolution using (-)-menthoxyacetic acid.

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RESOLUTION OF *THREO*-METHYLPHENIDATE

Field of the Invention

This invention relates to the resolution of *threo* methylphenidate *via* crystallisation of diastereomeric salts.

Background of the Invention

Methylphenidate was first prepared as a mixture of the *erythro* and *threo* racemates. US-A-2957880 discloses studies upon the two racemic mixtures, which revealed that the therapeutic activity resides in the *threo* diastereomer.

The resolution of *threo* methylphenidate can be achieved using the expensive resolving agent 1,1'-binaphthyl-2,2'-diylhydrogen phosphate, a process first reported by Patrick *et al* (The Journal of Pharmacology and Experimental Therapeutics, 241:152-158 (1987)), and subsequently used by other workers in the field (e.g. Aoyama *et al*, Journal of Chromatography, 494:420 (1989)). This is perceived to be a more efficient procedure than the method disclosed in US-A-2957880, wherein the corresponding amide of *erythro* methylphenidate (i.e. R-$CONR_2$ rather than R-CON_2Me) is resolved with tartaric acid prior to amide hydrolysis and equilibration at the benzylic centre, followed by esterification of the resultant *threo*-acid.

An improved resolution process is described in PCT/GB97/00185. Such a resolution can be combined with the racemisation described in PCT/GB97/00281.

Summary of the Invention

This invention is based upon the discovery that racemic *threo* methylphenidate can be resolved using inexpensive (-)-menthoxyacetic acid.

Description of the Invention

The process of this invention may be carried out under conditions that are generally known to those skilled in the art of classical salt resolution procedures. For example, a mixture of *threo* methylphenidate free base and 1 molar equivalent of (-)-menthoxyacetic acid in an inert organic solvent is heated and then allowed to cool; the resultant precipitate is filtered, washed with an appropriate solvent and dried to afford directly a salt enriched in 98% ee *d-threo* methylphenidate. This is a great improvement on the literature method using 1,1'-binaphthyl-2,2'-diylhydrogen phosphate, described by Patrick *et al*, *supra*, in which the first crystallisation gave a salt corresponding to 85-90%

ee material, and further recrystallisation of this material was necessary to raise the ee to 95-97%. The latter level of optical purity is achieved in the present invention in one crystallisation, with an overall higher yield. The method of this invention is therefore more efficient and more economical than the one described by Patrick *et al.*

The following Example illustrates the resolution of *threo* methylphenidate using (-)-menthoxyacetic acid.

Example

dl-threo methylphenidate (1.0 g, 3.7 mmol) was suspended in water (20 ml) and treated with caustic solution. The liberated free base was extracted with MTBE (3 x 25 ml), dried over $MgSO_4$ and evaporated to a light oil. This was dissolved in IPA (15 ml) and heated to 60°C. (-)-Menthoxyacetic acid (0.79 g, 3.79 mmol) in IPA (5 ml) was added. Heating was continued for a further 30 min and the mixture was gradually cooled to 10°C. The resulting white crystalline product was filtered off, washed with cold IPA and dried (0.85 g, 47% by weight, corresponding to 98% ee *d-threo* methylphenidate, as determined by chiral HPLC after salt cracking).

CLAIM

A process for preparing substantially single enantiomer *d-threo*-methylphenidate, which proceeds by means of a classical salt resolution using (-)-menthoxyacetic acid.

INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/GB 97/00643

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. PHARMACOL. EXP. THER., vol. 241, no. 1, 1987, pages 152-8, XP000612231 PATRICK K. S.; CALDWELL R. W.; FERRIS R. M.; BREESE G.R.: "Pharmacology of the Enantiomers of threo-Methylphenidate" cited in the application see page 153 ---	1
A	US 2 957 880 A (ROMETSCH ET AL.) 25 October 1960 cited in the application see example 6 --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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4 June 1997	20.06.97
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

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C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 4, no. 73 (C-012), 28 May 1980 & JP 55 038363 A (YOSHITOMI PHARMACEUT. IND.), 17 March 1980, see abstract	1
A	US 4 196 303 A (KANE ET AL.) 1 April 1980 see column 1, line 5-20	1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern: d Application No
PCT/GB 97/00643

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2957880 A	25-10-60	NONE	
US 4196303 A	01-04-80	NONE	